Remarks/Arguments

Claims 1-15 and 17 are pending in the application. Claims 16 and 18 have been cancelled by this amendment. Claims 1-9 and 15 have been withdrawn from consideration pursuant to a lack of unity objection. Claims 10-14 and 17 are therefore under consideration. Reconsideration is requested in view of the above changes and the following remarks.

Response to Section 112, 1st paragraph Rejection

Claims 10-14 and 16-18 have been rejected for lack of enabling disclosure in the specification. The Examiner alleges that the teachings of the specification regarding bacterial HSP complexes are not sufficient to enable a HSP complex from any protozoa, fungi or parasite. While applicant respectfully disagrees with Examiner's position, claims 10, 11 and 14 have been amended to recite that the heat shock protein complexes are obtained from the heat treatment of pathogenic bacteria. It is believed that this amendment overcomes the Section 112 rejection, particularly in view of the statement at page 7 of the February 16, 2005 office action to the effect that that the "specification has adequately described and provided method results and challenge experiments with vaccines comprising one or more complexes between a heat chock protein and an antigenic peptide fragment derived from the heat treatment of *bacteria*" (emphasis added). In addition, applicant offers the follow remarks in response to the Section 112 rejection.

Examiner submits under section 5 of the official action that "not all antibodies directed to heat shock proteins are protective" - that is that they can mediate an immune response which confers long term protective immunity. Examiner further submits under section 6 that the "specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity". However, what is particular about the instant invention as claimed is that the heat shock proteins which are used to complex with the peptides of the bacteria from which they are derived have been produced following the stressing of the pathogenic bacteria through the use of heat. The use of a heat stimulus to effectively "heat shock" the bacterial cell results in heat shock proteins being produced. These heat shock proteins then complex with peptide

fragments which are present within the bacteria. However, the heat shock proteins which are produced following the heat shock of the bacteria form complexes with a different profile of peptides than those which are complexed by heat shock proteins which are constitutively expressed by the bacteria, that is, by heat shock proteins which are produced under normal conditions in the absence of heat stress in order to perform the function of peptide processing and presentation within the bacteria.

Example 3 as provided at page 14 of the instant application provides a comparison of the peptides associated with the heat shock proteins which are produced in a bacteria following the stressing of the bacteria by means of heat shock, and peptides associated with heat shock proteins which are produced by the bacteria under normal conditions. Capillary Zone Electrophoresis (CZE) as detailed on page 15 of the instant application allowed for the analysis of peptides which were complexed to the induced and constitutive heat shock proteins. As detailed in the instant application, this analysis showed that the induced and constitutive heat shock proteins carried distinct families of associated peptides.

Further, it is detailed in the specification that immunization of mice with the heat-induced heat shock protein complexes gave significantly better immunity than immunization with heat shock protein-peptide complexes which are constitutively produced.

Further, Examples 3 and 4 of the instant application detail the induction of protective immunity against the pathogenic bacteria *Mycobacterium tuberculosis*, *E. coli* and *Salmonella typhimurium*. Applicant submits that these results, provided for three of the most commonly identified pathogenic bacteria, provide a sufficient teaching to support the enablement of the invention across the full scope of the invention as presently claimed.

Further, applicant refers to Examiner's comment at page 6 of the office action which state that "references cited above all showed antibodies to heat shock proteins, some of which were protective, while others were not protective. The prior art shows that heat shock proteins are

immunogenic but that immune responses to heat shock proteins are not predicatively protective against the pathogens to which they were induced". Applicant points out that the instant invention differs from the cited prior art in two important ways. Firstly, the heat shock proteins which comprise the heat shock protein-peptide complex which is used to induce an immune response according to the invention is comprised of heat shock protein molecules, the expression of which has been induced following the heat shock of the cell. Further, the long term protective immune response which is being mediated by the administration of the induced heat shock protein-peptide complexes of the present invention is caused not by the heat shock protein alone, but is due to the immunogenic properties of the heat shock protein-peptide complexes. This is specifically demonstrated by Example 4 of the instant application on page 16.

It is thus respectfully submitted that the invention as defined in the claims pending for consideration is adequately supported by the specification. Reconsideration and withdrawal of the 112 rejection is requested.

Response to Section 102 Rejection

Laminet et al.

Examiner has maintained the objection against claims 10, 11 and 13 under 35 U.S.C. 102(b) as allegedly being anticipated by Laminet et al. (EMBO Journal. 1990. 9(7): 2315-2319).

Under section 8 of the office action, Examiner submits that at page 7, lines 29-30 of the instant application, Applicant teaches the attainment of the invention based upon "the synthesis of stress protein occurs constitutively without the need to apply external stress". Examiner considers that this results in a product by process, and that the claimed composition therefore encompasses constitutively expressed compositions. However, applicant respectively points out, that where reference is made to the constitutive expression of heat shock proteins, this does not mean non-

induced heat shock proteins, but rather heat shock proteins which have been produced following the genetic modification of a pathogenic bacteria in order to turn on the genes encoding for heat shock proteins which would otherwise only be turned on following the application of stress to the bacteria such as a heat shock.

Under section 9, Examiner asserts that the claims do not require the claimed compositions to be more immunogenic than complexes formed from constitutively expressed heat shock proteins complexed to peptides. However, applicant submits that the claimed compositions have been differentiated over the compositions of Laminet et al. as the heat shock protein-peptide complexes of the present invention are induced following stressing with heat, while the compositions of Laminet are produced without such a specific heat shocking of the cells. The resulting complexes are different.

Examiner further makes reference to the extrinsic evidence of Del Giudice et al (1993) which teaches that heat shock proteins are immunogenic. However, as taught in Example 4 of the specification, the protective immunity provided by the present invention can be attributed to the immune response directed against the heat shock protein-peptide complex, and not just to the heat shock protein itself.

Claims 10, 11 and 13 are not anticipated by Laminet.

Srivastava (US Patent No 5,961,979)

Claims 10-14 and 16-18 have been rejected as allegedly anticipated by Srivastava (US Patent No 5,961,979). Claims 16 and 18 have been cancelled. Applicant will respond to the rejection as it relates to claims 10-14 and 17.

Examiner asserts that Srivastava discloses heat shock protein-antigenic peptide fragments that comprise a mammalian heat shock protein non-covalently bound to an antigenic peptide from a

bacteria. Examiner submits that the antigenic peptide fragment in the complexes of Srivastava are chemically synthesized to form complexes between and induced heat shock protein and an antigenic peptide. Such complexes are not, however, the same as or equivalent to the heat shock protein-peptide complexes of the present invention. Specifically, as described above, and in Examples 3 and 4 of the present specification, the induced heat shock proteins of the present invention conjugate with a different profile of peptides than those peptides which are associated with non-induced heat shock protein. In Srivastava, the step of chemically synthesizing and hence conjugating the heat shock protein and the peptide fragment, means that the formation of complexes of *induced* heat shock proteins with antigenic peptide fragments different from fragments complexed with non-induced heat shock proteins, is not performed.

Further, as taught at column 4, line 55 of Srivastava, the complexes of Srivastava are derived from a cell *infected* with the pathogen, and then heat shock protein-peptide complexes are extracted from the host cell. However, the present invention is directed to a vaccine formed from extracting, from a pathogenic bacteria itself, a complex of a heat shock protein and antigenic peptide.

Although Srivastava teaches induced heat shock proteins, it does not teach or provide the associated benefit of applying a heat shock to a pathogenic bacteria and then extracting the heat shock protein-peptide complexes therefrom in order to obtain a complex of enhanced immunity.

Applicant submits that the induced heat shock protein-peptide complexes of the invention are different from the Srivastava complexes. They are more immunogenic, and thus superior at mediating long term-protective immunity against the pathogen from which they are derived than the conjugated, synthetically manufactured complexes of Srivastava.

It is respectfully submitted that claims 10-14 and 17 are not anticipated by Srivastava.

Wallen et al. (US Patent No 5,747,332)

Claims 10, 11 and 13 have been rejected as allegedly anticipated by Wallen et al. Examiner submits that Wallen discloses compositions in accordance with the present invention. However, as in the case of Laminet et al., the production of the heat shock proteins by Wallen does not result from stressing of a cell by heat shock. Accordingly, the heat shock protein-peptide complexes which are provided by Wallen are different from the complexes of the present invention. The Wallen complexes are not as immunogenic as the heat shock protein-peptide complexes of the present invention.

Claims 10, 11 and 13 are therefore not anticipated by Wallen.

Yokata *et al.*

Claims 10, 11, 16 and 17 have been rejected as allegedly anticipated by Yokata *et al.*

The examiner considers the heat shock protein-urease fragment of Yokata *et al.* to be equivalent to the heat shock protein/peptide complex of the present invention. They are not. The 60kDa heat shock protein was found to complex to the beta subunits which form the urease enzyme. The heat shock protein is not complexed to the urease in the sense of the heat shock protein-antigenic peptide complex of the present invention. The beta subunits of the urease enzyme do not complex with the heat shock protein at the peptide binding site of the heat shock protein. Accordingly, when complexed with the urease beta subunit components, the heat shock protein does not participate in the antigen processing pathway of the cell. Thus, the beta subunit components will not be presented to the immune system, and accordingly an immune response would not be mounted against them. The heat shock protein/peptide complexes of the present invention are clearly different from the complexes of Yokata *et al.*

A key advantage of the present invention is that the induced heat shock proteins can bind a wide variety of antigenic peptides from a pathogenic bacteria, and when administered to a host, the large number of pathogens provide numerous antigenic targets against which an immune response can be directed. This results in broad immunity being mediated against the pathogenic

bacteria as the immune system can respond against many different epitopes. The use of only a single peptide when complexed to a heat shock protein would severely reduce the advantages conferred by the present invention.

It is respectfully submitted that claims 10-11 and 17 are not anticipated by Yokata *et al.*

Eschweiler *et al.*

Claims 10, 11, 16 and 17 have been rejected as allegedly anticipated by Eschweiler *et al.* The Examiner again considers the heat shock protein-urease fragment to be equivalent to the heat shock protein peptide complex of the present invention. This is not the case. The heat shock protein molecules of Eschweiler are not induced following the application of stress to the cell. Although Eschweiler mentions that heat shock proteins can be induced, there is no suggestion that they are induced by Eschweiler in the cited reference.

Further, although urease is seen to co-purify with the 60k protein which is thought to be a member of the heat shock protein family, this is not due to the urease being complexed to the heat shock protein by way of the heat shock protein peptide binding site, but due to the similarity in overall structure of the two proteins.

The advantage of the present invention is that the induced heat shock proteins can bind a wide variety of antigenic peptides from a pathogenic bacteria, and when administered to a host, the large number of pathogens provide numerous antigenic targets against which an immune response can be directed. This results in broad immunity being mediated against the pathogenic bacteria, as the immune system can respond against many different epitopes. The use of only a single peptide when complexed to a heat shock protein would severely reduce the advantages of such complexes.

For the foregoing reasons, claims 10, 11 and 17 are not anticipated by Eschweiler *et al.*

Austin *et al.*

Claims 10, 11, 16 and 17 have been rejected as allegedly anticipated by Austin *et al.* Although Austin discloses a complex of a bacterial heat shock protein and urease, the heat shock protein is not induced by the application of heat stress, as opposed to stress due to nutrient depletion. The complexes of Austin *et al.* are not the same as the complexes of the present invention.

Austin considers the structural similarity of urease and chaperonins such as GroEL and considers whether GroEL may interact with urease to assemble into a ring-shaped particle. The compound which results from the assembly of the ring-shaped particle is in no way similar or related to a complex of a heat shock protein and a peptide fragment. The function of a heat shock protein is to chaperone a peptide fragment of small length such that the peptide can be processed by the cell and exhibited to the immune system. This exhibiting allows the immune system to identify foreign protein and mount an immune response there against. The complexing of GroEL and urease plays no part in the antigen processing pathway, and there is no evidence to show that once complexed with urease that GroEL will perform its function of chaperoning broken down peptides.

GroEL does not interact with urease at the peptide binding site of the heat shock protein. Accordingly the nature of the interaction is completely different and distinct from the antigen processing function which is the subject of the present invention. The advantage of the present invention is that the induced heat shock proteins can bind a wide variety of antigenic peptides from a pathogenic bacteria, and when administered to a host, the large number of pathogens provide numerous antigenic targets against which an immune response can be directed. This results in broad immunity being mediated against the pathogenic bacteria as the immune system can respond against many different epitopes. The use of only a single peptide when complexed to a heat shock protein would severely reduce the advantages of such complexes.

Claims 10, 11 and 17 are not anticipated by Austin *et al.*

Conclusion

The claims remaining in the application are believed in condition for allowance. An early action toward that end is earnest solicited.

Respectfully submitted

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